Lecture note Renal Physiology(D)

Functional Anatomy of the Kidney:- There are 2 kidneys, one on either side, each weighing about 150 gms in an adult.

Each kidney is a bean shaped structure, showing an indentation in the middle of its medial side, called the hilius.
The renal artery, renal vein, ureter, lymphatics and the nerves either enter or exit via the hilus.

A longitudinal section of the kidney shows the following features:

1. Each kidney has two zones - Cortex (outer) and
   - Medulla (inner)
2. In the medullary zone, a few pyramid shaped structures, called renal pyramids, can be seen.
3. In between adjacent renal pyramids, there is a narrow mass of cortical tissue called the renal column.
4. Minor calyces merge major calyces 3-4 renal pelvis. The renal pelvis is the beginning of the ureter.

The term "urinary tract", means the following three structures all taken together: (1) ureter (2) urinary bladder and (3) the urethra.

The Nephrone:- A nephron is an anatomical and functional unit of kidney. Each kidney, in human beings, contain about 1.2 million nephrons.

nephron consists of:-

1. Renal corpuscle (also called malphigian corpuscle) and
2. The renal tubules. The renal tubule starts as a blind end called Bowman's capsule.

Renal corpuscle:- The renal artery enters the kidney → ultimately it drives and redivides and finally forms an afferent arteriole to the glomerulus → this afferent arteriole breaks up into a tuft of capillaries called glomerulus. These glomerular capillaries invaginate the Bowman's capsule (BC) and BC is the beginning of a renal tubule. The efferent arteriole, leads to the capillaries called glomerular capillaries. An individual glomerular capillary is extremely thin walled structure. Blood from these capillaries eventually drain into another arteriole called efferent arteriole from the glomerulus.

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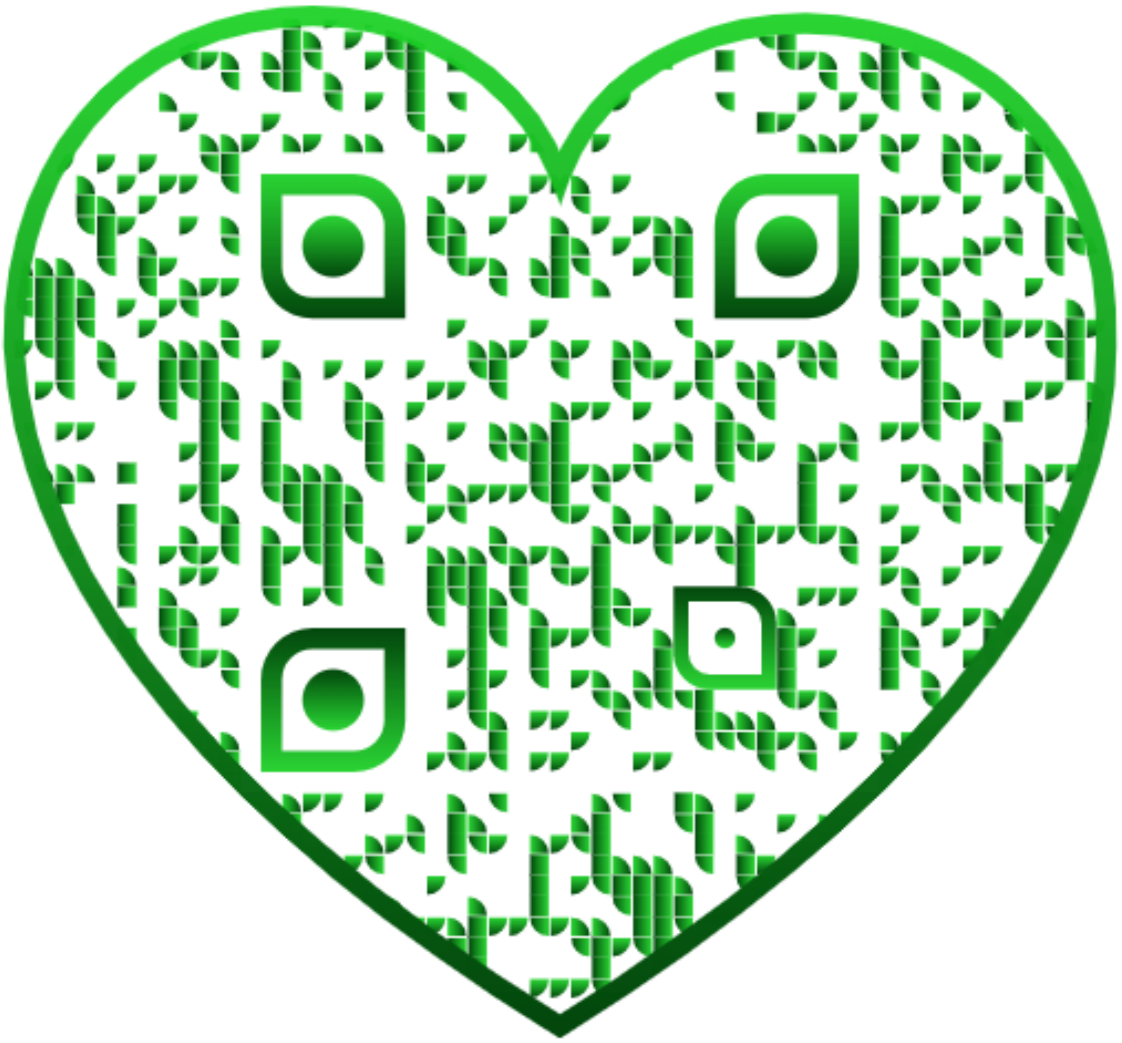

The efferent arteriole is narrower than the afferent arteriole → hence there is some accumulation of blood in the glomerular capillaries → this leads to high BP in the glomerular capillaries (high BP facilitates filtration).

Bowman's capsule (BC)

BC has 2 layers:
I. visceral and II. The parietal
In between these two layers, lies the bowman's space.

Filtering membrane: Blood of the glomerular capillaries is filtered and the ultra filtrate collects in the Bowman's space. The filtering membrane consists of:-

i. The capillary endothelium (contain flat and thin wall cells with pores) of the glomerular capillary
ii. Epithelium of the visceral layer of the bowman's capsule.
iii. The basement membrane between the two layers

The Renal Tubule

Parts:

- bowman's capsule
- proximal tubule (PCT and pars recta)
- Loop of Henle (thin descending, the ascending limb)
- The thick ascending limb courses upwards through the cortex – passes between the afferent and efferent arterioles its glomerulus – then it continues as the DCT.
- The DCT open into the collecting tubule (CT), which again opens into the renal pelvis.
- The lining epithelium of PCT is taller columnar cells with brush border. The brush border increases the cells surface area for maximum material transport across the cell membrane.
- In the collecting ducts, there are two types of cells:
  I. the principal (p) cells and
  II. I cells. P cells are concerned with water and Na+ reabsorpton while I cells are for reabsorption of H+ and HCO-3 and play strong role in acid-base balance of the body.

Types of Nephrons

1. Superficial or cortical nephron (CN) and
2. Juxta medullary nephron (JMN)

differences between the two types of nephrons:

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1. The loop of Henle of JMN is very long-penetrates deep into the medulla. Where as the loop of hence of CN is short.
2. In the CN, the efferent arteriole from the glomerular capillaries form peritubular capillaries whereas the efferent arteriole from the glomeruli af JMN form vasa recta.
3. The JMN are mainly concerned with Na and H_2O conservation and concentration of urine. These nephrons are particularly for animals living in desert habitats where water is scarce.

Juxta Glomerular Apparatus (JGA)

The thick ascending limb of the loop of Henle passes between the afferent and efferent arteriole of its own glomerulus. In doing so, it comes very close to the afferent arteriole. Here in the tunica media of the afferent arteriole, myoepitheloid cells (juxta glomerular cells-JG cells), containing granules are present. These granules are the storage form of an enzyme, rennin, i.e., from these granules renin is secreted. Renin plays an important role in maintaining BP, Na^+ conservation and K^+ excretion. The lining of epithelial cells of ascending thick limb of the loop of Henle show some histological peculiarities. These cells of the thick ascending limb constitute the "macula densa". Adjacent to this segment of the tubule, in between the afferent and efferent arterioles, lie lacis cells. Juxta glomerular apparatus = JG cells + macula densa + lacis cells.

Renal blood vessels

Each minute, about 1.2 litres of blood flows through the two kidneys. That is, about 25% of the resting cardiac output flows through the two kidneys.
Renal artery → interlobar arteries → arcuate (arcuate = like a bow) artery → radial artery → afferent arteriole → peritubular capillaries/vasa recta.

Note:

1. The capillary BP in the glomerular capillaries is high.
2. The BP in the peritubular capillaries is very low; the BP is thes capillaries is about 10mmHg and the colloidal osmotic tension high. This facilitate movement of reabsorbed materials from t surrounding tissue fluid into the capillary blood.
3. Velocity of flow of blood in the vasa recta is very slow. This he the medullary gradient to be preserved and urinary concentratio made possible.

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Nerve supply

The kidneys are supplied by ANS, both sympathetic and parasympathetic. Sympathetic fibers supplying the kidney, consists of both
I. efferent and II. Afferent fibers. The efferent fibers supply the:

- Smooth muscles of the blood vessels notably the afferent arteriole to the glomerulus and
- JG cells. Stimulation of sympathetic leads to activation of JG cells.

The receptors of the sympathetic nerve ending at the afferent arteriole are of the $\alpha 1$ variety. JG cell stimulation causes production of rennin and rennin ultimately causes production of angiotensin II, thus vasoconstriction-hypertension.
Sympathetic fibers also supply the renal tubules, notably the PCT and the thick ascending limb of the loop of Henle.
Afferent sympathetic fibers are the fibers via which the pain sensation from the kidney is conveyed, ultimately, to the brain (so that pain from the kidney is perceived).

Regulation of Renal Blood Flow

1. Sympathetic simulation and nor adrenalin (NA) cause constriction of afferent arteriole to the glomerulus → this results in diminished blood flow to the glomerular capillaries – fall of filtration pressure (FP).
2. Dopamine, DA, is a vaso active amine. DA, at a certain concentration, causes renal vasodilation. Therefore to increase blood flow in the kidney, intravenous DA transfusion can help a lot.
3. Angiotensin II, causes constriction, chiefly of the efferent arteriole from the glomerulus.

- GFR doesn't change with mild or moderate changes of perfusio pressure (= BP) in the renal artery. It should be understood that th GFR does-not change even when (I) there is mild or moderate ri of hydrostatic pressure with in the ureter, or. (II) when these mild or moderate change of colloidal osmotic tension, of plas (because of the renal autoregulation).

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Mechanism of Formation of urine

Brief Summary

1. In the glomerulus, the plasma of blood is filtered-because of both anatomical and physiological convenience. The filtrate is called "ultrafiltrate". This ultrafiltrate (glomerularfiltrate) collects within the Bowman's capsule. The filtrate enters PCT – onwards from now it is called tubular fluid.
2. The amount of glomerular filtrate is great, about 180 litres/day. In the renal tubules, the tubular fluid undergoes massive reabsorption, concentration and acidification. Some new materials are also added to it. The final product, amount being normally, only 1.5 litres/day, highly concentrated and acidified, is the urine which collects into the renal pelvis.

Mechanism of Filtration

1. The filtering membrane is extremely thin (facilitates filtration).
2. The BP in the glomerular capillaries is very high. This facilitates the filtration. However, some forces oppose the glomerular capillary BP. Yet, the resultant pressure, called the "effective filtration pressure" is sufficiently high (causes filtration of plasma).
3. the permeability of the glomerular filtering membrane is good.

GFR Varies as $(Pc - Pb - \pi c)$

Where

Pc = the glomerular capillary BP (60 mmHg)

Pb = the hydrostatic pressure in the Bowman's space (20mmHg)

πc = colloidal osmotic tension, (CDT) of the glomerular capillary blood (30mmHg)

he EFP,

= Pc – (Pb + πc)

= 60 – (20 + 30)

= 10mmHg

e value of CFR: In normal healthy young adults, the value of GFR about 120 ml/min (= 180L/day). However, in the elderly the G value falls. In ESRD (end stage renal disease), The value of GFR become as low as 10ml/min and such patients can remain alive if they are dialysed regularly or receive kidney transplantation.

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The Glomerular Filtrate: This is an ultrafiltrate of plasma, ie, it contains everything the plasma has excepting, in healthy state, the plasma proteins. Note:

i. a very small quantity of albumin is filtered (b/s negatively charged and is insignificant)
ii. Urine even normally contain proteins (very small quantity) but that comes from (mainly) degenerating cells living the renal tubules.

- In various diseases, the GF contains protein chiefly albumin. In such conditions urine contains proteins (mainly albumin) and the condition is called albuminuria, or protein uria.

Tubular Functions: The major functions of the renal tubules include:

i. reabsorption
ii. secretion
iii. concentration and
iv. acidification of tubular fluid. The final product is urine.

Filtered load – Px X GFR
Px = conc. of the substance in the plasma

Eg. GFR = 180 L/day
Px of Na = 140 mmoles/liter

Filtered load = (140 x 180) mmoles = 25000 mmoles/day (this means total amount of Na filtered by the kidneys or 575 gm/day).

Table 1. Some typical values (approximate values)

Substance	Plasmaconc (Px) (mmole/L)	Filtered load /day Px X GFR	Fractional reabsorption in %
Na^+	142	25,000 (=575gms)	Over 99%
K^+	4	700 (=27gms)	90%
HCO_3^-	24	4,000 (240gms)	99.5%
Glucose	5	900 (=160gms)	100%
Water		170/180 liters	99%

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Functions of PCT:

1. PCT reabsorbs about 2/3 of the GF. That is, if the GF is 130 ml/min, the PT reabsorbs about 85 ml/min.
2. Reabsorbed materials:
   - Inorganic = Na^+, HCO^-_3, K^+
   - Organic – glucose, a-a;, lactic acid, citric acid, uric acid, urea
   - Massive reabsorption of water
   - K^+ after its absorption by PT, some K^+ is secreted into the tubule at the DCT.
3. In the PT- glucose is totally reabsorbed
   bulk of Na^+ is reabsorbed
4. H^+ ions are actively secreted by the PT

Sodium Reabsorption: from the lumen of the PT to inside of the living epithelium. This movement is down hill movement because in the lumen, conc. of Na^+, is high as compared inside the luminal cells. However, this movement is aided by either a co-transporter (for a. as and glucose) or an exchanger proteins (for H +ion).

After the Na^+ has entered the interior of the cell (either by the help of the cotransporter or counter transport), the Na+ ion is pumped out by of the cell by Na^+K^+ - ATP ase (actively on the basolateral portion of the luminal cells).
The Na^+ ion from the tissue fluid enters the peritubular capillaries.

Bicarbonate Reabsorption and H^+ secretion

The PT also reabsorbs HCO_3^- ions and secretes H+ions. H+ secretion also occurs in the DCT and collectingduct but mechanism of H+ secretion in these regions is not identical with that in the PT.

Reabsorption of Glucose by PT

- Normally, virtually the entire amount of glucose is reabsorbed in the PT. The maximum ability of the PT cells to reabsorb glucose is 375mg/min. However, when the glucose level is 180mg/100ml, glucose appears in urine (glucosuria). The reason is some nephrons cease to reabsorb much earlier-and from these nephrons glucose begins to appear in the urine.

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Water Reabsorption by The PT

The GFR in 24 hrs is about 180 liters. In 24 hrs, only about 1.5 liters of urine is formed. Obviously huge quantity of water is reabsorbed. About 2/3 of this water is reabsorbed in the PT.
A concentration gradient between the tissuefluid and tubular fluid created following the co-transport of Na+ with glucose and a-as. Facilitate passive reabsorption of water interstitium.

Secretion by The PT

PT also secretes some substances besides H^+ such as organic compounds (Paramino hippuric acid, creatinine, drugs like penicillin and salicylates, some iodinated dyes. These organic substances are secreted by the pars recta of the PT.

Function of the loop of Henle and the DCT

The functions of the distal segment (Henle + distal nephron) include;

i. concentration of urine
ii. further reabsorption of Na+, Cl-, and water
iii. acidification of urine
iv. Secretion of K+, Ca+2, Mg+2, some drugs.

Permeability

1. The thin descending limb of the loop of Henle is extremely permeable to water but only very slightly permeable to Na+.
2. The thick ascending limb is permeable to Na+ but not to water.
3. The early part of distal tubule is impermeable to water but permeable to Na+.
4. The collecting duct becomes water permeable only when it is subjected to ADH.

- In the deepest zone of medullary interstitium the tonicity rises usually about 1200 mosmols/kg H_2O because of NaCl and urea. This medullary gradient remains undisturbed because of circulation in vasa recta (JMN contribute a lot for concentrating urine).

Concentration of urine: mechanism

1. Fluid iso osmotic with plasma (osmolality about 280 mosmols) is delivered from the PCT to the thin descending limb of the loop of Henle.
   - As the fluid moves down, water is reabsorbed.
   - Impermeable to Na+ and the fluid becomes concentrated.

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2. Nextly the tubular fluid reaches the ascending limb.
   - the thick segment rigorously reabsorbs Na+ and is accompanied by Cl- and K+ ions
   - this segment is impermeable to water
   - As this fluid looses Na+, Cl- and K+ but no water lose, it becomes more diluted.
   - The interstitium becomes more concentrated.

3. Hypotonic fluid (diluted) is delivered to the distal tubule.
4. In the early distal tubule, reabsorption of Na+ (but not water) continues – causes further dilution of the luminal fluid.
5. Finally, the fluid enters the collecting duct.
   - because of effect of ADH, the permeability of the collecting duct to water increases hence, water is reabsorbed massively to the concentrated medullary interstitium until equilibrium is attained.

Role of Vasa recta

Blood flow velocity of the capillaries, called vasarecta, is extremely sluggish. As the blood descends down the vasarecta through the medullary interstitium, the solutes from medullary intestidium enter the vasarecta and the blood of the vasarecta becomes very very hypertonic (concentrated).

↓

The vasarecta makes a "U" bend (along the loop of Henle) and moves towards the outerzone of medulla. Here, the modullary interstitium is isosomotic with plasma but the blood of vasarecta (venerecte) is very hypertonic → the solutes leaves the venerecte and enters the medullary interstitium.

Mechanism Na^+ Reabsorption in the DCT: Role of aldosterone

1. In the thick ascending limb
   From the lumen, one ion of Na^+, one ion of K^+, and two ions of Cl^- are concomitantly bound to a co transport protein in the luminal membrane of the living cell.

2. *Distal tubule:* In the luminal cellmembrane of the liningcell, a NaCl co transporter is present, in which one Na^+ ion and one Cl^- ion bind concomitantly → subsequently both the ions enter the cell (Nacl co transporter is different from $Na^+K^+2Cl^-$ co transporter).

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3. *Collection duct*: In the luminal membrane of the lining cells of CD, Na+ channels are present through which Na+ ions enter → then pumped out by Na^+K^+ -ATPase.

- Role of aldosterone: Causes:
  - i. Greater reabsorption of Na+ ions from the tubular fluid.
  - ii. Greater secretion (extrusion) of K+ into the tubular fluid of the DCT and collecting duct.

Role of ADH (antidiuretic hormone)

- Osmolality of tubular fluid in the collecting duct is 100m osmols/kg H2O
- Osmolality of the fluid in the interstitium is −300m osmols/Kg H2O (in the outer medulla), and 1200 m Osmols/KgH_2O (in the deeper part of the medulla.)
- This concentration gradient between tubular fluid and the in terstitium facilitate massive reabsorption of water from the tubular fluid in to the interstitium.
- ADH causes opening of water channels on the CD (collecting duct) so greatly facilitate reabsorption of water. In total absence of ADH, water reabsorption from the CD is greatly curtailed but not abolished.
- Diuretics are drugs which cause increased amount of urine formation.

Acidification of urine

Metabolic processes produce phosphoric and sulfuric acids (plus little amount of other acids). With an average diet, the H^+ ions generated by these acids (the H^+ load; 100m moles per day) must be removed to avoid acidosis. This removal of H^+ ions (generated by metabolism), is done by the renal tubules. Therefore, kidney failure produces, renal metabolic acidosis.

H^+ ions are extruded (actively by a proton pump) by the lining cells of the renal tubules a process called H+ ion secretion at proximal tubule and distal nephron, particularly the colleting duct.

- Acidification of tubular fluid occurs in distal nephron.
- In the PT the H+ forms H_2CO_3 and thus strong fall of PH is prevented. In the distal nephron the H+ ions are buffered by (a) phosphate buffer or (b) amnionia. Ammonia (NH_3) is produced by the tubular cells from glutamine. Glutamine (amine) loses NH_3 to become glutamic acid with the help of tubular cell enzyme. The NH_3 being lipid soluble enters the lumen of the tubule where it reacts with H^+ to become NH^+_4 ion and is excreted via urine.

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Increase NH_4^+ excretion occurs during acidosis as a compensatory mechanism.

K^+ Excretion

About 27 gms of K^+ appears in the GF in a day (filtered load). About 2-4gms of K^+ are excreted via urine per day.
Much of the filtered load of K^+ is reabsorbed in the PCT. In exchange of each ion of Na+ which are reabsorbed by the distal tubular cells, either one K^+ ion or one H^+ are secreted in to the lumen.

Aldosterone:
- Increases Na^+ reabsorption
- K^+ excretion from the distal nephron. Hence excessive aldosterone can cause Na^+ accumulation + hypokalemia (low plasma K^+ concentration)

Ca^{++} Re-absorption

Serum contains about 10mg of Ca/100ml. But about half of this is bound with protein and thus non-filterable and hence does not appear in the GF. In 24 hr period the filtered load is about 9gm of which about 200mgms are excreted via urine. The rest is reabsorbed at the:

- PT
- Ascending limb of the loop of Henle
- Distal tubule and CD

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Lecture note: ReNin-angiotensin system[RAS]

Under suitable conditions, renin is secreted from the JG cells of the afferent arteriole to the glomerulus. The renin acts on a plasma protein called angiotensin syntherized by the liver in response to cortisol and estrogen stimulation). Ultimately the angiotensinogen is converted into angiotensin II (by renin and ACE- angiotensinogen covertig enzyme).

The major actions of angiotensin II include :

i. elevation of system BP
ii. Increased secretion of aldosterone leading to increased reabsorption Na+ and excretion of K+ by the renal tubules
iii. Development of thirst, etc

It is now possible to block the generation of angiotensim II by a group of drugs called "ACE inhibitors" (very popular drugs used to treat hypertension)

Stimulants for Renin secretion

2. When the B.P in the afferent arteriole to the glomerulus is low, renin is secreted.
3. Sympathetic stimulation increases renin secretion
4. Delivery of NaCl is the macula densa region

When more NaCl in the macula densa of the tubular fluid reach, the Cl ion produce a signal in the macula densa when ultimately causes reduction of renin secretion → less angiotensin II secretion → less adosterone → more Na+ excretion via urine → diuresis.

- Other functions renin
  - ADH and ACTH secretion
  - Stimulate sympathetic system
  - Causes contraction of mesangial cells (These again cause kinking glomerular capillaries and ↑GFR)
- Atrial Natriuretic protein ANP (BNP in brain)

ANP is stored is the atrial musculature, when there is Na+ retention leading to expansion of ECF, hypertension, the atria become distended due to excessive blood → stretching of a trial muscle → release of ANP.

Action:

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- Opposite to angiotensin II
- Causes – hypotension
  - Natriuresis (diuresis with excretion of excess Na+)
- ANP cause mesangial cells to relax →widening of glomerular Capillaries →more blood flow → GFR → natriuresis .

ones vital in renal function
RAS
ANP
Aldosterone
ADH
Parathormone – ↑ca retention and PO4 reabsorption in PCT in a state of hypovolemia (volume depletion), and low BP, →↓ GFR→ less NaCl reach maculadensa → renin secretion → in aldosterone secretion →↑ Na+ reabsorption by the DCT and CD → correction of volume depletion.

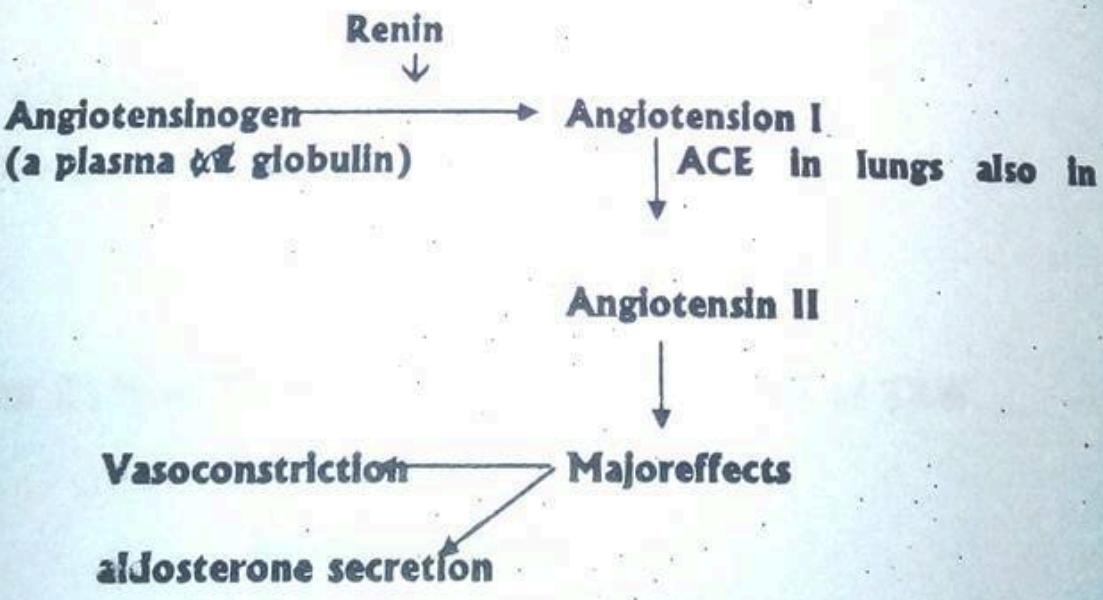

Fig. 1 Renin-angiotensin system (RAS)

nctional Tests

function tests include:

e examination. Kidney diseases are associated with abnormalities rine. However, an abnormality of urine does not necessarily

2. Blood analysis
Waste products:
- Blood urea (normal) – 15-40mg/100ml
- Serum creatinine (normal value) 0.6 to 1.5mg/100ml this value rises in renal failure

In some renal disease, concentration of plasma protein, notably concentration of plasma albumin falls. In severe oliguria, Concentration. Serum K+ may be high (a dangerous sign). In advanced renal failure, acidosis may develop.

3. Different renal clearance tests show abnormality. Concept: Consider an *example*: In a person urinary out put is 1ml/min and this 1ml of urine contains 15mg of urea. This means, the person is removing 15mg of urea/min.

Again, his blood urea conc, let us presume, is 26mg/100ml. Therefore, 15mg of urea was contained in $^{15}/_{26}$ x 100ml or 57 ml blood.

This can be viewed as follows:

In this person, the urea contained in 57ml blood is removed completely by the kidneys in every minute. Or urea clearance in this person is 57ml/min.

- Similar clearance tests can be performed such to check renal function such as Insulin clearance, creatinine clearance test, and para amino butric acid (PABA) tests.

- In many kidney diseases the GFR falls. GFR is thus an index of ren function. Normal value GFR is about 130ml/min. In severe ren disease it may be as low as 10m/min. In old persons, the GFR val shows a fall.

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Lecture note: Regulation of Plasma Osmolarity ,ECF volume & Serum Electrolyte Balance

I. Plasma Osmolality

Value: 280 to 295 m Osm/ liter

II. Total body water (TBW), accounts for about 75% of fat free body weight (lean body mass). However, if fat of the body is not excluded from the weight, in an average man, water accounts for about 52% of the body weight. Proportionately, infant and children have more water (and hence their body is soft and malleable). Proportion of body water falls in old age (this is one important cause of wrinkles in the old persons).

Table 1. distribution of body water

Body water compartments, BWC

[BWC]

↓ ↓

ECF (about 31% of TBW) **ICF (about 69% of TBW**

↓ ↓

Plasma **Interstitial fluid**

(about 24% of TBW)

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Table :2 Distribution of electrolytes

All values are m moles liter		
Cations	Plasma	ICF
Sodium	140	10
Potassium	4	160
Calcium	2	
Magnesium	1	13

Maintenance of plasma osmolality

This is done by:

(1) ADH and

(2) Thirst mechanism

Examples:

1. Imagine there is extreme water deprivation. Yet some 500 ml of urine (obligatory volume) will have to be formed and in tropical country some sweating will occur; both these represent water loss from the body dehydration develops. Compensatory mechanisms:

a) Plasma osmolality, due to water loss, rises – osmoreceptors of hypothalamus stimulated – ADH secreted vigorously – water loss saved, tries to lower the plasma osmolality.

b) Thirst develops – more water drinking this water dilutes the plasma.

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11. Another example is Na accumulation in the body. Excess Na+ intake → plasma solute concentration rises → plasma osmolality rises →ADH secretion → water conservation→plasma dilution (but note the plasma volume, now, expands). Also thirst develops → more water drinking → correction of plasma hyperosmolality.

Conversely

Plasma dilution (eg. By drinking of huge amount of water) →fall of plasma osmolality → no ADH secretion → excess urine and free water of urine (solute free water in the urine) increases → osmolality corrected.

Volume homeostasis: ECF volume (plasma + tissue fluid) is regulated by:

1) altering the content of Na+ in the plasma and
2) controlling the water excretion from the body, by aldosterone – ADH- AN mechanism. Examples:

a. Hypovolemia: In sudden severe hypovolemia, shock (hypovolemic shock) develops and the compensatory include: Hypovolemia → activation of renin – angiotensin axis →production of aldosterone → increased reabsorption of Na+ from renal tubules → solute concentration Of plasma rises →↑ plasma osmolarity →ADH secretion H2O reabsorption → ECF volume expansion.

Also, hypovolemia when severe, via atrial receptors, causes vigerous secretion of ADH – water conservation – ECF expansion

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b. Hyper volemia: This causes secretion of ANH(ANF)/ANP by the heart → natriuresis + diuresis. Also, inhyper volemia, renin angiotensin production stops → no aldosterone → renal reabsorption of Na^+ falls → loss of water via urine.

Electrolyte Balance

I sodium loss

Clinically this is seen in conditions like

1) Massive use of loop diuretics causing loss of massive Na+ and water
2) Severe diarrhea, cholera (water loss + massive Na+ loss) and the patient is freely drinking water

Chain of events:

Na loss → fall of plasma osmolarity → no ADH secretion – water loss via urine – results:

1) correction of hypo osmolality of plasma as well as,
2) Hypovolemia. This hypovolemia can cause hypovolemic sho (symptoms:low BP- tachycardia→ signs of sympathetic o activity.

   Also, hypovolemia causes RAS activation → more aldoste →Na conservation.

II. Sodium excess

Common clinical conditions, while this can be seen, include;

i) some diseases of the kidney (faulty Na excretion)

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ii) Heart failure (reduction of GFR leading to excess Na reabsorption)

iii) Hyper aldosteronism and so on

hain of events: Na accumulation →plasma hyper osmolality → rise ADH secretion →↓ urinary loss of water → ECF expansion + rrection of plasma hyper osmolality.

mptoms: Those due to ECF (including plasma) expansion: pertension edema (even pulmonary edema)

ote, Hypervolemia causes:

- Stoppage of RAS activity and
- ANP Secretion. Result: (1) no aldosterone +(2) natriuresis due to ANP – removal, of extra Na from the body. Therefore, plasma hyperosmolality, at first, is corrected by plasma dilution (hyper volemia) but ultimately the excess Na is removed by ANP and lack of aldosterone.

I. Potassium loss

inically this may develop in:

i) Hyperaldosteronism

ii) Severe diarrhea

iii) Excess use of diuretics, etc.

erum k+ is restored from outflux of K+ from ICF (cause k+ ↑ in

).

mptoms: K+ deficiency in ICF can cause abnormality of resting embrane potential – an early sign is weakness of the muscles.

. Potassium excess

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Excess K^+ concentration causes abnormal resting membrane potential abnormality of excitability and conductivity.

Also, recall, K^+ and Ca^{++} are mutually antagonistic – therefore, excess K^+ conc. Leads to fall of Ca^{++} causing poor contractility of myocardium.

Result abnormal excitability for heart

3) fall of cardiac contractility – sudden cardiac death can occur

4) ECF volume depends on total body sodium content. If the total Na content - ECF expands but the Na conc. In the serum plasma remains normal.

Blood volume: Blood volume at different ages:

Normal values- in newborn, this is about 80ml/kg body wt.

- At about 15 years, this is 70ml/kg body wt.
- In adult males it is nearly 5 liters
- In adult non – pregnant females it is nearly 4 liters

Hemoconcentration and Hemodilution

1) When the ECF volume shrinks but there is no loss of formed elements of blood (RBC+ WBC + platelets), hemoconcentration develops. In hemoconcentration, HB conc, RBC count rise. This condition is seen typically in severe diarrhea burn, and acute water deprivation. Hemoconcentration is also seen in poly cythemia.

2) Hemodilution is seen typically in severe anemia, severe generalized edema, etc.

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Chain of events following acute hemorrhage

8 During of immediately after acute hemorrhage there hemodilution as because both the formed elements and plas lost.

With in few hours, the tissue fluid enters the compartment and now hemodilution develops. The entry fluid is due to the fact that blood loss causes fall of capill

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Acid Base Balance

The concept of PH: The H^+ concentration of blood is $10^{-7.4}$ meq/L instead of writing the cumbersome expression each time viz, the concentration of H^+ in blood is $10^{-7.4}$ meq/L, one can express it by saying P^H of blood is 7..4. That is,

$$PH = \log \frac{1}{H^+ \text{ ion concentration per liter}}$$

Notes: If the H^+ concentration of blood increases, then it becomes more than $10^{-7.4}$ Let us presume after such increase, it has become $10^{-7.1}$. The PH of blood now is 7.1, that is as the numerical value of PH falls, the solution (eg. Blood) becomes more and more acid. Conversely, in alkalosis, the value rises.

The PH of ECF and ICF must be maintained with in a very narrow range.

The pH of blood (and of ECF as a whole) in health is 7.4 (range 7.36 to 7.42). If the blood pH is less than 7.36, the condition is called acidosis, while if it is more than 7.42, the condition is called alkalosis. It is not possible to remain alive if the pH of blood is out side of 7.0 to 7.7 for long period.

The ICF PH is probably 7.2

Maintenance of PH is so important because all body enzymes act best at a particular pH. If the pH is outside this optimal pH, then enzyme efficiency deteriorates → cellular functions deteriorate. Thus, in acidosis, CNS functions, myocardial contractility, vascular tone begin to deteriorate early and there is death unless the PH value of blood is restored.

Sources of H^+

1. The metabolism of sulfur containing amino acids (methionine cysteine – cystine) produces sulfuric acid (H_2SO_4), sulfuric acid dissociates strongly and produces free H^+ ions Metabolism of mucleic acid, phospholipids produce large amount of phosphoric acid (H_3PO_4) which also dissociates strongly to generate H^+ ions. There H^+ must be removed otherwise acidosis will result. Incidentally, the amount of H^+ generated by the above mentioned metabolic processes is about over 50meg/day.

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2. On the other hand krebs cycle produce huge amount of CO_2 → this CO_2 eventually produces H_2CO_3. H_2CO_3 is a weak acid, dissociates poorly, yet because of the tremendous amount of CO_2, the H^+ generated (the H^+ lode) in this way is considerable (about +12000meg/day). H_2CO_3 is called volatile acid because H_2CO_3 breaks into H_2O and CO_2 → the CO_2 is expired out.

Therefore, normally the H^+ load received by the body is considerable and this H^+ load must be removed, otherwise acidosis will result.

The H^+ load is tackled as follows:

1. Immediately, H^+ ions, are captured by buffers → buffers prevent fall of PH, but while doing so the buffers themselves loose their efficiency.
2. After wards the H+ are removed by the lungs or by the kidneys and the buffer system is regenerated.

On the other hand where the concentration of H^+ in the blood (rather in the ECF) fall, the pH of blood rises → alkalosis results For example, excessive vomiting → heavy loss of HCL rich in gastric juice → loss of H^+ ions from the body → rise of blood pH → alkalosis. In such cases the buffers try to prevent rise of blood pH; the lungs and kidneys together preserve H^+ ions.

Buffers: Buffers are substances which when present in a solution resist the change of pH when H^+ ions are added or removed from the solution.

Blood buffers: Major buffers of blood are:

1. Carbonic acid – bicarbonate system
2. Hb and
3. Protein

In the interstitial fluid the Hb is totally absent and the protein is nearly absent, so that, carbonic acid bicarbonate system becomes the all important buffer.

ICF buffer: In cells except RBCs the major buffers are:

1. Protein and
2. Phosphate buffer

Note:

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1. Blood plasma also contains small amount phosphate so its importance as a buffer in blood is small
2. In the ICF, importance of phosphate buffer is great
3. In the urine, phosphate buffer has got a vital role

MOA of buffers: The carbonic acid – bicarbonate buffer system (also called the bicarbonate buffer system) This buffer system contains H_2CO_3. H_2CO_3 can dissociate into H^+ and HCO_3 ions and can be expressed as:

$$H_2CO_3 \rightleftharpoons H^+ + HCO_3 \quad \text{---------- (1)}$$

When H^+ ions are added (eg. When H_2SO_4 produces free H^+ ion and appears in the blood), these H^+ ions (from H_2SO_4) combine with the HCO_3 ions to produce H_2CO_3 (the equation shifts to the left). Now, H_2CO_3 being a very weak acid, it (= the H_2CO_3) dissociates (into H^+ + HCO_3) very poorly, so that, in the ultimate analysis, only few H^+ ions are added and the fall of PH of the solution (in which the buffer is present) is either nil or marginal. Had there been no buffer, the fall of PH would have been great. Note, as H^+ ions are being added, although the PH does not alter (or alters only marginally), the HCO_3 ions "bicarbonate reserve" begins to disappear (fall). When the blood bicarbonate reserve becomes nil, then the buffer loses its efficiency and now slight addition of H^+ ions will cause a sharp fall of blood pH.

The H_2CO_3 thus produced, breaks down to H_2O and CO_2 → the CO_2 is breathed out.

On the other hand, in alkalosis, ie, where H^+ ions are withdrawn from the blood, the dissociation of H_2CO_3 of eg. 1 is accelerated → more H^+ ions are generated by the buffer system so that rise of PH is prevented. However, there is a rise of HCO_3 ions.

Other buffers, like Hb, protein etc behave in a similar way. Viewed in one way, carbonic acid – bicarbonate buffer system is the most important buffer system in blood because the system is tied up with respirator system and is quickly adjustable. For example,

When there is addition of excess H^+ (acidosis), more H_2CO_3 (in eg. 1) formed → respiration is stimulated → CO_2 of H_2CO_3 is exhaled and H excreted via urine. Thus, the H^+ are quickly removed.

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Role of Lungs

During: Acidosis

Consider there is accumulation (due to, say, renal failure where H+ ions are not properly excreted by the kidney) of strong acids (sulfuric/phosphoric) → more H^+ enter blood → carbonic acid - bicarbonate system buffers absorb the initial assault.

The H^+ of the strong acids are captured by HCO_3^- and H_2CO_3 formed (H_2CO_3 as stated above does not lower PH appreciably) → the acidosis stimulates respiration CO_2 of H_2CO_3 breathed out (and H_2O) escapes via urine → excess H^+ disposed.

Alkalosis

In alkalosis, hypoventilation develops → reduction of removal of CO_2 of H_2CO_3 → H_2CO_3 accumulates→ prevention of loss of H^+ ions.

Role of Kidneys

The kidney:

i. Secretes H+
ii. Reabsorbs HCO_3^- (thus maintaining HCO_3 reserve)

H^+ ions are secreted in the PCT, DCT, and collecting duct (CD). For every H^+ secreted in the PCT, one HCO_3 ion is reabsorbed in the PCT. About 95% of the filtered load of the HCO_3 is reabsorbed in the PCT. The rest, nearly 5% reabsorbed in the DCT and CD.

Factors that increase the H^+ secretion or HCO_3 reabsorption in the PCT include:

1. acidosis
2. rise of PCO_2 (as in pulm. hypoventilation)
3. hypokalemia

In the CD aldosterone causes increased H+ secretion (this can lead to alkalosis in Cushing's syndrome – a condition characterized by excess cortisol production).

In acidosis, the NH_3 synthesized by the kidney tubules, captures H^+ to become NH_4^+ and is excreted via urine.

Additional note – Acidosis (metabolic or respiratory)

Causes: retablic acidosis

1. Accumiation of B hydroxyl butryric acid – aceto acetic acids (in diabetic keto acidosis, DKA)
2. Renal acidosis
3. lactic acidosis due to excess intake of phenformin (an oral antidiabetic drug)
4. Severe diarrhea (pancreatic juice rich in $HaHCO_3$ is massively lost via feces), etc.

Compensatory mechanism:

1. Blood buffers absorb the immediate shock (H^+)
2. The acidosis causes stimulation of respirations → removal of CO_2 → fall of PCO_2
3. Kidneys secrete excess H + ion, reabsorbs all HCO_3, NH_3 synthesis

Alkalosis

It can be (i) metabolic or (ii) respiratory. Cause of metabolic alkalosis include severe vomiting → leading to excessive loss of HCL, ie, H^+ ions.

Compensatory mechanisms:

1. Bicarbonate buffer system prevents sharp rise of PH; the H_2CO_3 breaks in to H^+ and HCO_3 and the H^+ ions, thus gained, preven sharp rise of pH but HCO_3 content rises.
2. This is a fall is respiratory derive → rise of PCO_2. This tries elevate H_2CO_3 conc. In plasma.
3. Urinary secretion of H^+ via kidney is severely curtailed. HC excretion by kidney increase.

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